

Case Study Title:	Defining Process Design Space	Case No.	RMWG-07
GMP System Impacted:	Quality		
Introduction / Background	<p>Risk assessment of the manufacturing process is a key activity in product development, especially as a supportive tool in Quality by Design (QbD).</p> <p>In this case study, a drug product has been formulated with different variants each with a different dissolution profile ranging from slow to fast. While an <i>in vitro in vivo</i> correlation (IVIVC) evaluation was not possible due to some product specific pharmacokinetic factors, the profiles of all of the formulations were similar. The dissolution method was already known to be over-discriminatory and the slowest dissolution profile from the range of formulation variant studies was set as the slowest dissolution profile that would be acceptable and this profile would serve as the surrogate test for the quality of the clinical product in processing studies. In other words, the design space for clinical quality would be a product with a faster dissolution profile than the slowest variant.</p> <p>To ensure a full understanding of all potential influences to the design space a full risk assessment of the manufacturing process was conducted to ensure areas of greatest risk were appropriately considered and controlled, as warranted.</p>		
Defining the Risk Question	<p>The risk question developed for the subject case study is:</p> <p><i>What are the critical input and processing variables for the product that would affect the product quality based on the design space?</i></p>		
Selecting a Risk Assessment Method	<p>A manufacturing process for a drug product usually consists of many steps, each with potentially multiple variables requiring evaluation. The selected risk assessment method must produce a quantitative output that describes the level of risk relative to other risks being assessed. As an aid to a likely complicated risk assessment effort, the resulting data should also be organized in such a way that that a simple visual summary can be produced.</p> <p>The risk method selected for the subject case study is:</p> <p style="text-align: center;">Failure Mode Effect Analysis (FMEA)</p>		

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Risk Assessment (Risk Identification, Analysis and Evaluation)

Risk Identification -

The risk assessment team assigned to this initiative first prepared a list of all operations and associated supporting systems that had potential impact on product quality. During this stage of the Quality Risk Management (QRM) process, no processes were excluded simply because the process was perceived as “low risk” (reference Table 2 – *QRM Output* for a partial list of the risk areas identified).

Risk Analysis and Evaluation -

The Risk Analysis stage of the QRM process estimates the potential harm(s) associated with each potential risk. The analysis may be qualitative or quantitative in nature, or a combination of the two.

In this case study, the analysis used was quantitative. The risk score or risk product number (RPN) was determined by multiplying the scores for probability, severity and detectability:

$$\mathbf{RPN = Probability\ Score \times Severity\ Score \times Detectability\ Score}$$

The ranking definitions for Probability, Severity, and Detectability were developed prior to commencing any actual assessment and are summarized in Table 1 – *Scoring Scheme for Probability, Severity, & Detectability*.

After the risk areas were identified, subject matter experts worked to evaluate each risk area and list corresponding failure modes and associated failure effects for each risk area. Subsequently, probability, severity, and detectability were determined using the scoring criteria in Table 1. The results were collated to Table 2 and then reviewed to ensure consistency and accuracy. The final output was published for risk prioritization.

Each line item from the assessment was ranked as either a low, intermediate, or high risk depending on the calculated RPN value. A RPN of < 40 was considered a low risk; a RPN of 40 – 99 was identified as an intermediate risk; and a RPN of 100 or greater was defined as a high risk. Risk rankings took into consideration the overall RPN value as well as how significant the issue under assessment was to the development of the product. In many cases, mitigating the larger RPN issues also resulted in a decrease in the calculated RPN for areas with lower identified risks.

To facilitate a better understanding and management of the results defined by Table 2, a color-coded chart was developed to correlate risk-assessment results to anticipated tablet quality, categorized by specific unit processes (Figure 1). By summarizing the results in this manner, the project team was able to see and communicate how the identified risks were inter-related and prioritized (by RPN) for risk mitigation.

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Table 1- Scoring Scheme for Probability, Severity, and Ability to Detect

Probability	Score
1/>10000	1
1/1000	2
1/100	3
1/10	4
1/<10	5

Severity	Score
Deviation	1
Reanalysis, passed	2
Rejected sub batch or batch	3
Stop in production flow	4
Product recall	5

Detectability	Score
Before unit operation	1
During unit operation	2
During subsequent unit operation(s)	3
Finished product testing	4
Detected by customer	5

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Table 2 - QRM Output

Risk area	Failure mode	Failure effect	Risk analysis			
			P	S	D	RPN
RAW MATERIALS						
Drug substance	Changes in particle size or properties, e.g. shape, surface energy, bulk properties	Changes in dissolution performance, thus impacting on clinical performance	4	5	5	100
Excipients	Increasing the level of binder	Slow tablet disintegration leading to altered clinical performance	4	5	5	100
	Decreasing the level of disintegrant	Impeded tablet disintegration leading to altered clinical performance	4	5	5	100
	Magnesium stearate variability, leading to impeded wetting of drug particle	Changes in dissolution behaviour leading to altered clinical performance	3	5	5	75
	Variability in amount of diluents or properties within specified grade	Changes in granule properties resulting in altered disintegration/dissolution profile	2	5	5	50
PROCESS						
Dry mixing	Insufficient mixing; poor blend uniformity	Large range of active ingredient content throughout the batch	2	3	4	24
Wet granulation	Failure to control granulation end-point; Over- granulation	Decreased granule porosity, decreased water ingress and decreased dissolution rate. Adverse effect on clinical quality	4	5	5	100
	Excessive water added or holding the wet mass for significant time before drying	Decrease in disintegrant performance; wicking and swelling during wet massing. Decreased dissolution rate and consequent adverse effect on clinical performance.	3	5	5	75
Dry milling	Incorrect dry milling parameters, e.g. impeller speed, screen size	Effect on granule size leads to altered dissolution and adverse effect on clinical performance	3	5	5	75
Lubrication	Blending time too long, leading to hydrophobic coat of lubricant around granules	Decreased dissolution rate leads to adverse effect on clinical performance	3	5	5	75

(P=Probability; S=Severity, D=Detectability)

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Figure 1 - Color Summary Chart of Results in Table 2

	API & Excipient Variability	Dry Mixing	Wet Granulation	Fluid Bed Drying	Dry Milling	Lubrication	Compression	Coating	Packaging
Dissolution	UNKNOWN or HIGH RISK	LOW RISK	UNKNOWN or HIGH RISK	LOW RISK	INTERMEDIATE RISK	INTERMEDIATE RISK	INTERMEDIATE RISK	LOW RISK	LOW RISK
Disintegration	UNKNOWN or HIGH RISK	LOW RISK	UNKNOWN or HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Identification	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Assay	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Content Uniformity	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Appearance - capping	INTERMEDIATE RISK	LOW RISK	UNKNOWN or HIGH RISK	INTERMEDIATE RISK	INTERMEDIATE RISK	UNKNOWN or HIGH RISK	UNKNOWN or HIGH RISK	LOW RISK	LOW RISK
Appearance - picking	INTERMEDIATE RISK	LOW RISK	UNKNOWN or HIGH RISK	LOW RISK	LOW RISK	UNKNOWN or HIGH RISK	UNKNOWN or HIGH RISK	LOW RISK	LOW RISK
Appearance	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	INTERMEDIATE RISK	LOW RISK
Friability	LOW RISK	LOW RISK	INTERMEDIATE RISK	LOW RISK	INTERMEDIATE RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Stability - chemical	INTERMEDIATE RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Stability - physical	LOW RISK	LOW RISK	INTERMEDIATE RISK	INTERMEDIATE RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Microbiology	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK

	- LOW RISK
	- INTERMEDIATE RISK
	- UNKNOWN or HIGH RISK

<p>Risk Control</p>	<p>Assessed risks were reduced by identifying the unit operations or procedures where the RPN was calculated above a certain threshold and developing corresponding risk mitigating strategies to lower the overall calculated risk level. This calculated RPN value was a relative number, based on other assessed risks, and was developed using a set of predefined definitions on severity, probability and detectability. Following the implementation of mitigating actions to reduce the perceived high risk areas, the RPN values were re-calculated to ensure that the projected risks were appropriately reduced.</p>
<p>Risk Documentation and Control</p>	<p>The risk analysis was reviewed by management and experts in Quality Risk Management assigned to the project. The knowledge gained through this risk assessment was shared with the employees at the company's other development sites as well as externally in a series of industry forum presentations. In addition, the learnings from this risk assessment have been incorporated into current development projects and will be institutionalized for future use.</p>

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Risk Review

In following the company policy for quality and quality systems, a report describing the rationale, risk assessment process, action plan, and conclusions were forwarded to the appropriate internal quality groups for future follow-up (e.g. audit, PAI risk analysis).

To follow the feedback loop as recommended in ICH Q9, work was carried out to mitigate the risk of the items with high RPNs (action plan implementation). After this work was completed, the group reviewed the results of the mitigation actions and some batches manufactured after the risk assessment and convened a second quality risk assessment primarily focusing on the areas with high RPNs. Other risk areas with initial lower RPN values were also assessed to determine any additional impact (positive or negative) resulting from mitigating actions taken for the highest prioritized risk areas. The results of this follow-up assessment were published in the same format as Table 2 and were distributed to the stakeholders as in the original risk assessment.

A third review was carried out sometime after the implementation of the risk mitigation actions discussed above. This third check, somewhat removed from the initial assessment and mitigating efforts, was performed to further ensure that the conclusions and actions from the risk assessment were correct.